PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P008500WO ATM		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/00974	07.03.2003	07.03.2002

International Patent Classification (IPC) or both national classification and IPC
G01N33/68

Applicant
CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LI.. et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.10.2003	18.02.2004

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/00974

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-49 as originally filed

Claims, Numbers

1-24 received on 23.12.2003 with letter of 18.12.2003

Drawings, Sheets

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 18-24
	No:	Claims	2-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: SWAAK A J G ET AL: 'Serum levels of soluble forms of T cell activation antigens CD27 and CD25 in systemic lupus erythematosus in relation with lymphocytes count and disease course.' CLINICAL RHEUMATOLOGY, vol. 14, no. 3, 1995, pages 293-300, XP009011883 ISSN: 0770-3198

   D2: KNAUF W U ET AL: 'Serum levels of soluble CD23, but not soluble CD25, predict disease progression in early stage b-cell chronic lymphocytic leukemia' LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 27, no. 5/6, 1997, pages 523-532, XP009011890 ISSN: 1042-8194

2. Article 33(2) PCT

   Document D1 discloses the monitoring of the serum levels of soluble forms of T cell activation antigens CD27 and CD25 in systemic lupus erythematosus and the correlation of said levels with the disease course. This document appears to be novelty destroying for claims 2-17.

   Document D2 discloses the monitoring of the soluble forms of CD23 and CD25 to predict the disease progression in lymphocytic leukemia. This document appears to be novelty destroying for claims 2-17.

   For the reasons above, claims 2-17 do not meet the requirements of Article 33(2) PCT.

3. Article 33(3) PCT

Present claim 1 differs from documents 1 and 2 in that the soluble CD (sCD) fingerprint comprises the levels of five or more sCDs, instead of two sCDs as in documents D1 and D2. The technical problem to be solved by claim 1 is the provision of an indicator of disease and disease progression in an individual. As explained in the disclosure, page 21, the solution proposed by the invention is based on the provision of fingerprints/profiles of sCDs measured in body fluids of the individual, a preferred fingerprint comprising the levels of five or more sCD molecules. However, from the disclosure of the invention it appears that the limitation to a fingerprint of five sCD molecules is just an alternative selected from several possible numbers of sCDs to be measured for the fingerprint. Furthermore, only claim 1 is limiting the sCD fingerprints to comprise the levels of five or more sCDs. Therefore, in the light of D1 and D2, claim 1 is not considered to be inventive.

Claims 18 to 24 (see further paragraph 4 bellow) are not considered to be inventive. In the light of the teaching of D1 and D2, an attempt to inhibit the production of the sCDs released in each specific condition in order to treat the molecular mechanism underlying the condition appears to be obvious.

Therefore, claims 1-24 do not meet the requirements of Article 33(3) PCT.

4. Article 6 PCT

Claims 18 to 24 are not supported by the description, contrary to the requirements of Article 6 PCT. The application does not disclose any concrete molecule or example for therapy of one or several diseases administrating inhibitors of the production of one or more sCDs. The present disclosure seems to merely speculate with the possibility of treating various different conditions with theoretical inhibitors of the production of sCDs.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/00974

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WOOLFSON A ET AL: "ALTERNATIVE SPLICING GENERATES SECRETORY ISOFORMS OF HUMAN CD1" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 91, no. 14, July 1994 (1994-07), pages 6683-6687, XP001152660 ISSN: 0027-8424 the whole document --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2003	11/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreno de Vega, C

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 03/00974

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	SWAAK A J G ET AL: "Serum levels of soluble forms of T cell activation antigens CD27 and CD25 in systemic lupus erythematosus in relation with lymphocytes count and disease course." CLINICAL RHEUMATOLOGY, vol. 14, no. 3, 1995, pages 293-300, XP009011883 ISSN: 0770-3198	1-17
Y	the whole document	1-24
X	BIGLINO, A. ET AL: "Serum cytokine profiles in acute primary HIV-1 infection and in infectious mononucleosis" CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, vol. 78, no. 1, January 1996 (1996-01), pages 61-69, XP002245772	1-17
Y	the whole document	1-24
X	KNAUF W U ET AL: "SERUM LEVELS OF SOLUBLE CD23, BUT NOT SOLUBLE CD25, PREDICT DISEASE PROGRESSION IN EARLY STAGE B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA" LEUKEMIA AND LYMPHOMA, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 27, no. 5/6, 1997, pages 523-532, XP009011890 ISSN: 1042-8194	1-17
Y	the whole document	1-24
X	RIBBENS C ET AL: "Increased synovial fluid levels of soluble CD23 are associated with an erosive status in rheumatoid arthritis (RA)." CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 120, no. 1, April 2000 (2000-04), pages 194-199, XP009011870 ISSN: 0009-9104	1-6,8-17
Y	the whole document	1-24

CLAIMS

1. A shed CD (sCD) fingerprint comprising the levels of five or more sCDs wherein the sCD fingerprint represents one or more disease states.

2. A method of generating a shed CD (sCD) fingerprint of one or more disease state/s comprising the step of measuring the levels in parallel of more than one shed CDs from one or more individuals and collating the data.

3. A sCD fingerprint according to claim 1 or a method according to claim 2 wherein the disease state is any one or more selected form the group consisting of: infectious, neoplastic, autoimmune, metabolic, immunological, degenerative, psychological, psychiatric, iatrogenic, inflammatory, drug or toxin related, vascular, traumatic and endocrine diseases.

4. A sCD fingerprint or a method according any preceding claim wherein the disease state is any one or more selected from the group consisting of the following: infection, Bence Jones Proteinuria, Chronic Myeloid Leukemia, Colorectal cancer, chronic renal failure, Crohn's Disease, Diabetic Nephropathy, Cardiac pathology, Infection, Liver damage, Lymphoma, macrocytic anaemia, Prostate Cancer, Oligoclonal Banding and Pulmonary Embolism/Deep Vein Thrombosis and appendicitis.

5. A sCD fingerprint according to claim 1 or claim 3 or claim 4 or a method according to claim 2, claim 3 or claim 4 wherein the sCDs referred to comprise two or more selected from the group consisting: CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40 and their homologues present in other mammalian or non-mammalian species.

6. A method according to any of claims 2 to 5 wherein the sCD levels are measured in samples of one or more body fluids from an individual.

7. A method according to claim 6 wherein the body fluid is serum.

8. A method according to any of claims 2 to 7 wherein sCD levels are measured using one or more methods selected from the group consisting of: immunoassay and flow cytometry.

9. A method according to claim 8 wherein sCD levels are measured using any one or more method selected from the group consisting of the following: multiplexed particle flow cytometry, chip based monoclonal antibody technology, chips comprising engineered antibodies, non protein agents which bind to one or more sCDs.

10. A method for predicting the presence of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more reference sCD fingerprint/s.

11. A method for detecting the presence of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more reference sCD fingerprint/s.

12. A method for detecting the extent of one or more disease states in an individual comprising the step of comparing one or more sCD fingerprint/s generated from that individual with one or more reference sCD fingerprint/s.

13. A method for assessing the progression of a disease state in an individual comprising the step of comparing the sCD fingerprint of an individual at two or more periods during the life-span of the disease.

14. A method for assessing the effect of one or more agent/s on one or more disease states in an individual comprising the step of comparing a sCD fingerprint of an individual at two or more different time periods.

15. The use of a sCD fingerprint to assess the effect of one or more agent/s on an individual.

16. A method for sub-categorising a sCD fingerprint profile comprising the steps of identifying within one disease category one or more group/s of sCDs wherein each group of sCDs exhibits common characteristics distinguishing it from any other group within that disease category.

17. A sCD database comprising pathological and/or normal sCD fingerprint patterns.

18. A method for treating one or more diseases comprising the step of inhibiting the production of one or more sCDs within an individual.

19. A method according to claim 18 wherein the one or more sCDs are any one or more of those selected from the group consisting of the following: CD14, CD25, CD31, CD44, CD50, CD54, CD62E, CD62L, CD86, CD95, CD106, CD116, CD124, CD138, CD141, CD40L, CD8, CD23, CD30, CD40.

20. A method according to claim 19 wherein at least one sCD is sCD1.

21. A method according to claim 18 or claim 19 wherein the production of one or more sCDs is inhibited by the use of one or more CD specific alternative splicing inhibitors.

22. A method according to any of claims 18 to 21 wherein the disease is any one or more of those selected from the group consisting of the following: tumourigenesis, infection, vascular disease, endocrine disease.

23. The use of an inhibitor of the production of one or more sCDs in the preparation of a medicament for the treatment of disease.

24. The use according to claim 23, wherein that use exhibits any one or more of the features of claims 18 to 22.